

Case Report

Use of recombinant factor VIIa in a thrombocytopenic patient with spontaneous intracerebral haemorrhage

Intracerebral haemorrhage (ICH) accounts for 10–15% of all cerebral strokes. After ICH, thirty-day survival rate is approximately 60%, but 80–90% of the survivors will suffer severe neurologic impairment (1, 2). Primary ICH originates from the spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy while secondary ICH occurs in a minority of patients in association with vascular abnormalities, tumours and impaired coagulation (3).

Intracerebral bleeding has been considered a monophasic event limited by clotting and tamponade effect of the surrounding tissues. However, it was recently reported that intracerebral haemorrhage expands over time because of a persisting bleeding from the primary source and a mechanical disruption of the surrounding vessels (4, 5). Therefore, the prevention of haematoma enlargement by ultra-early haemostatic therapy ought to be considered a primary issue in the management of ICH patients (6). Bearing this in mind, recombinant activated factor VII (rFVIIa) is very attractive because of its pan-haemostatic effect (7). After its initial registration for the treatment of bleeding episodes in haemophilia patients with inhibitors to factor VIII or IX (8), rFVIIa has also been used to control massive bleeding in patients with other inherited or acquired coagulation defects (9, 10), including coagulopathies associated with liver disease (11), trauma and surgery (12). Furthermore, rFVIIa can induce a thrombin burst by the binding to activated platelet surface, regardless of Tissue Factor exposition (13). This mechanism compensates for the lack of platelet adhesion and aggregation observed both in congenital platelet function disorders and in thrombocytopenia (14–17).

In this report, we describe the use of rFVIIa in a thrombocytopenic patient with ICH undergoing emergency craniotomy for hematoma evacuation.

A 52-year-old man was involved in a motor vehicle accident when he lost consciousness while driving his car. After admission to the Accident and Emergency Department, a CT scan of the head showed a frontal polar and left basal intracerebral haematoma of about 65 cm³ with a moderate mass effect. The remaining radiological and physical evaluation were unremarkable. Medical history evidenced a recently diagnosed Idiopathic Thrombocytopenic Purpura (ITP), treated with anti-CD20

monoclonal antibody (Rituximab). On ICU admission, the patient was unconscious with a Glasgow Coma Scale score (GCS) of 8. Full blood count showed marked thrombocytopenia (platelets 18 x 10⁹/l), with otherwise normal coagulation tests. We decided to treat ITP with high-dose intravenous immunoglobulin (0.4 g/kg body weight) and high-dose dexamethasone (40 mg/day) followed by a single donor unit of platelets. One hour after ICU admission, we performed a cerebral angiography that excluded any cerebral vessels abnormality. A subsequent brain CT scan showed an increase of the mass effect exerted by the haematoma; the patient was then taken for emergency craniotomy. Because of persisting thrombocytopenia (platelets count 30 x 10⁹/l), a 90 µg/Kg dose of rFVIIa was administered immediately before surgery. The surgical procedure lasted 3 hours and neurosurgeons reported a complete evacuation of the haematoma with good brain decompression and a dry surgical field without signs of coagulopathy. Total blood loss was approximately 300 ml and neither packed red blood cells nor platelets were infused. On ICU re-admission, laboratory tests showed a stable haemoglobin concentration, normal coagulation parameters and low platelets count (28 x 10⁹/l). Eight hours later, after sedation withdrawal, neurological condition deteriorated (GCS score of 5) and an urgent CT scan evidenced a new hematoma in the region beside the surgical focus. At that time platelet count was 44 x 10⁹/l and after consultation with the neurosurgeon, reintervention was excluded. We thus decided to repeat rFVIIa (90 µg/kg), intravenous immunoglobulin (0.4 gr/kg body weight) and dexamethasone (40 mg/day for three further days) followed by a further single donor unit of platelets. In the following days the platelet count gradually increased up to normal values and brain CT scans showed a progressive reduction of the haematoma. The patient was discharged from ICU 15 days after admission with a mild motor strength impairment in the right arm, aphasia and a good level of consciousness (GCS score of 13, National Institute of Health Stroke Scale of 11). After 58 days he was discharged from the hospital with mild aphasia and a National Institute of Health Stroke Scale score of 8.

This case suggests that rFVIIa can be considered an effective therapeutic option to control bleeding during neurosurgical procedures in thrombocytopenic patients. In fact, in spite of a low platelet count, blood loss during surgery was limited and neurosurgeons reported a dry surgical field. Other clinical experiences reported the successful use of rFVIIa in thrombocytopenic patients with overt bleeding (15–17). In addition, the recently completed Phase II NovoSeven Intracerebral Hemorrhage (ICH) trial demonstrated the effectiveness of rFVIIa in the initial management of selected ICH patients (18). However, to the best of our knowledge this is the first case that describes the use of rFVIIa to improve haemostasis in thrombocytopenic patient undergoing neurosurgery.

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Conventional therapy for ITP (i.e. intravenous immunoglobulins and steroids) was immediately started in our patient. This usually increases platelet count up to normal level in a few days. While such a therapy was probably effective to prevent late re-bleeding episodes, its delayed onset is unacceptable in an emergency setting. In these situations, rFVIIa can be used as a 'bridge therapy' to quickly improve haemostasis and to gain the time needed for platelets to increase by standard therapy (i.e. immunoglobulins and steroids).

We report an early re-bleeding episode after surgery, but it probably occurred when the effect of the first rFVIIa dose was fading. Therefore, we can hypothesize that re-bleeding would not have occurred if we had continued rFVIIa. This is in accordance with the therapeutic strategy applied by Vidarsson et al. (15) in a 27-year-old woman with severe thrombocytopenia and life-

threatening bleeding. They administered rFVIIa (90 µg /Kg) every 2 hours five times and then 4-hourly for four more times, with a very rapid clinical improvement despite the low platelet count. In conclusion, in treating thrombocytopenic patients, the need for repeated doses of rFVIIa should be always considered in order to ensure a good haemostatic response in spite of platelet defect.

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